Persistent generalized periodic discharges: A specific marker of fatal outcome in cerebral hypoxia

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Abstract: OBJECTIVES Electroencephalography (EEG) is one of the methods used in predicting the outcome after cerebral hypoxia. In this study we aim to evaluate the significance of generalized periodic discharges (GPD) as a prognostic marker. METHODS We retrospectively analyzed the medical histories of patients, who underwent an EEG after cardiac arrest during the time period from 2005 to 2013 at the University Hospital Zurich. All EEGs were re-interpreted using the 2012 American Clinical Neurophysiology Society (ACNS) classification for intensive care unit (ICU) EEGs. RESULTS Out of 131 patients, in which an EEG was recorded after cardiopulmonary resuscitation, 119 were included in our study. The average interval between cardiac arrest and EEG-recording was 3.8±3.0days (range: 0-14days). Persistent GPDs (i.e. GPDs more than 24h after the event) were found in thirty-two (26.9%) of the patients initial EEGs. The appearance of persistent GPDs preceded fatal outcome in 100% of all cases (vs. 69.0% in the non-GPD-group, $p<0.0001$). CONCLUSION Among other encephalopathic markers in EEG persistent GPDs are a highly specific prognostic marker of fatal outcome in patients with hypoxic encephalopathy. SIGNIFICANCE Using standardized EEG interpretation, this study identified persistent GPDs as a specific prognostic marker in post cardiac arrest syndrome.

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Persistent generalized periodic discharges: A specific marker of fatal outcome in cerebral hypoxia

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Abstract

Objectives: Electroencephalography (EEG) is one of the methods used in predicting the outcome after cerebral hypoxia. In this study we aim to evaluate the significance of Generalized Periodic Discharges (GPD) as a prognostic marker.

Methods: We retrospectively analyzed the medical histories of patients, who underwent an EEG after cardiac arrest during the time period from 2005 to 2013 at the University Hospital Zurich. All EEGs were re-interpreted using the 2012 American Clinical Neurophysiology Society (ACNS) classification for intensive care unit (ICU) EEGs.

Results: Out of 131 Patients, in which an EEG was recorded after cardiopulmonary resuscitation, 119 were included in our study. The average interval between cardiac arrest and EEG-recording was 3.8±3.0 days (range: 0 - 14 days). Persistent GPDs (i.e. GPDs more than 24 h after the event) were found in thirty-two (26.9%) of the patients initial EEGs. The appearance of persistent GPDs preceded fatal outcome in 100% of all cases (vs. 69.0% in the non-GPD-group, $p<0.0001$).

Conclusion: Among other encephalopathic markers in EEG persistent GPDs are a highly specific prognostic marker of fatal outcome in patients with hypoxic encephalopathy.

Significance: Using standardized EEG interpretation, this study identified persistent GPDs as a specific prognostic marker in post cardiac arrest syndrome.

Highlights:

1. GPDs were seen in about a quarter of the EEGs performed in patients who had suffered circulatory arrest
2. The occurrence of persistent GPDs is almost invariably associated with fatal outcome
3. The occurrence of GPDs was not associated with the (non-)use of pharmacologic sedation

Keywords: Intensive care EEG, GPD, Hypoxic encephalopathy, Post cardiac arrest syndrome

Introduction

Cerebral hypoxia is the main reason of impairment or death after an initially successful cardiopulmonary resuscitation (CPR) (Neumar et al., 2008). Estimating the patients' individual prognosis after CPR remains a difficult task. Especially in comatose patients, Somatosensory evoked potentials (SSEPs) (Zandbergen et al., 2006), biomarkers like neuron-specific enolase (NSE) (Zandbergen et al., 2006), cerebral imaging (e.g. Howard et al., 2012) electroencephalographic (EEG) recordings (e.g. Hofmeijer et al., 2015, Rossetti et al., 2010) have been suggested as means to obtain an estimate. Apparent advantages of EEG are its non-invasive character and its sensitivity with regard to cortical function.

Neurophysiologists base their predictions on various patterns associated with encephalopathy. Among them are background slowing, burst-suppression patterns (Hofmeijer et al., 2014) and/or generalized periodic discharges (GPDs), which are commonly seen after severe cerebral hypoxia.

Overall GPDs are a rarely seen pattern – according to monocenter studies occurrence rates range from 0.15% in all patients (Kuroiwa and Celesia, 1980) up to 3.8% in inpatients (Foreman et al., 2012) - and are deemed an unspecific marker of encephalopathy. On the other hand they are a relatively common finding in patients after CPR. A retrospective study (Yamashita et al., 1995), described GPDs in 23% of the patients after CPR, while a more recent study reported an occurrence in roughly one third of the patients with postanoxic encephalopathy (Rossetti et al., 2009). They are thought to be associated with poor outcome (e.g. Bauer et al., 2013, Pedersen et al., 2013).

However few studies exist, that evaluated the specificity of GPDs as a separate entity (Ribeiro et al., 2015, San Juan et al., 2009; Yemnisci et al., 2003; Husain et al., 1999). Furthermore, there has until recently been no consensus on a terminology describing periodic patterns. For example there is no clear distinction between GPDs and generalized subtypes of non-convulsive status epilepticus (Rossetti et al., 2007, Trinka and Leitinger, 2015). Not until 2012 a proposal of terminology for describing intensive care unit (ICU) EEGs was presented by the American Clinical Neurophysiology Society (ACNS) (Hirsch et al., 2013).

Through this retrospective study we aimed to reevaluate the significance of GPDs as prognostic markers using the standardized classification provided by the ACNS (Hirsch et al., 2013). We intended to analyze clinical data of in-hospital patients, who suffered cerebral anoxia due to cardiac arrest and had an EEG afterwards.

We addressed the following questions: how often did GPDs occur in these EEGs, and to which extent did their occurrence correlate with an unfavorable outcome. In order to evaluate

their prognostic value we compared GPDs with other encephalopathic changes in EEG. Furthermore we analyzed whether other clinical variables such as age, sex, duration of anoxia or the use of antiepileptic drugs (AED) altered the outcome.

Material and Methods

Selection of the study cohort

We selected EEGs of adult patients (male and female, age > 16 years) in our database of ICU EEGs, who suffered a definite episode of cardiac arrest between 2005 and 2013.

The main inclusion criterion was:

> (1) EEG within two weeks after cardiac arrest of at least three minutes length. (2) Full documentation of the patient's history, EEG, drugs taken during the time of EEG monitoring, diagnosis and general outcome after one month. (3) No neurodegenerative disease known before cardiac arrest. (4) No severe traumatic brain injury.

The exclusion criterion was:

> (1) The patients declined to the use of their data. (Though patients were not specifically asked for consent for this retrospective study, some patients generally declined to the use of their data for study purposes)

Information of the outcome was gathered from all available medical reports (discharge reports from intensive care unit (ICU) and/or reports from the rehabilitation clinic, which were very detailed in most cases). The outcome was assessed one month after CPR as described by Yamashita et al (Yamashita et al., 1995) and measured in following terms: death within one month; severely impaired, - i.e. requiring continuous care in all aspects of life corresponding to modified Rankin Scale 4 and 5; slightly and moderately affected (i.e. at least able to communicate and not fully dependent on help) = mRS 1 – 3.

After 2008 patients were increasingly treated with mild hypothermia (34°C) for at least 24 hours in the aftermath of cardiac arrests if the breakdown of circulation lasted longer than 10 min and if there were no contraindications. EEGs were always performed after the warming up.

Standard EEG study procedure:

All EEGs were recorded according to the 10–20 system with needle or pad electrodes. In addition, a one-channel electrocardiogram was recorded via additional skin surface electrodes. EEG traces were evaluated through bipolar longitudinal and transverse montages, as well as through average reference montage. During EEG recordings of comatose patients, standardized acoustic stimuli (loud clicking sounds) and painful tactile stimuli were performed by EEG technicians. Standard trigger maneuvers (hyperventilation and/or intermittent photic stimulation) were not routinely performed in the ICU.

Our routine EEGs complied with the requirements of the German Society for Clinical Neurophysiology (DGKN 2006) and had a minimum standard length of 20 minutes.

The EEG system used was a Nihon Kohden EEG-1100 EEG Recorder. Data were reviewed using 'Megis EEGFocus' software. All EEGs were evaluated and interpreted a posteriori by the study investigators and were consequently reclassified according to the standardized criteria provided by the ACNS (Hirsch LJ et al 2012., see below). The reviewers of the EEG data were blinded for the outcome.

Interictal epileptiform activity as a separate entity was diagnosed applying the criteria of IEAs provided by (Gloor, 1977).

If present, the results of cerebral imaging (either CT or MRI) were also included into the dataset.

Terminology and Statistical analysis:

All EEGs were re-interpreted according to ACNS Critical Care EEG Terminology 2012 version (Hirsch LJ et al, 2013): For each patient, we analyzed the following parameters: (1) background activity (alpha-, theta-, delta-dominant), (2) background voltage (normal, low, suppressed), (3) spontaneous reactivity/ reactivity to stimuli, (4) occurrence of periodic discharges or rhythmic delta waves, their distribution (lateralized/generalized) and their frequency (in the case of GPDs we defined a low frequency threshold of 1/30Hz, as there was none given in the ACNS criteria), (5) occurrence of burst-supression patterns, (6) occurrence of other graphoelements indicating encephalopathy, - including non-periodic generalized discharges with blunt triphasic morphology and classic interictal epileptiform discharges. As all EEGs showing GPDs were recorded at least 24 hours after resuscitation, we consistently used the term "persistent GPDs", as there are reports on dramatic changes of the dominating EEG patterns already in the first 24 h after resuscitation (Spalletti et al., 2016, Sivaraju et al., 2015).

The frequency of any pattern was described in following standardized terms: continuous, abundant, frequent, occasional and rare.
For convenience EEGs showing discontinuous or no discernible background were categorized as "disturbed background continuity".
Clinical and statistical parameters sampled were: (1) underlying illness leading to the cardiac arrest, (2) Glasgow coma scale (GCS) at the time of the recordings, (3) approximate length of cardiac arrest, which was defined as time from arrest to return of spontaneous circulation (ROSC), (4) timespan between the event and the EEG recording, (5) the sedative and/or antiepileptic medication given, (6) the outcome one month after resuscitation as mentioned above.

In patients, who had more than one EEG during hospitalization, all follow-up EEGs during the time span of one month were also reinterpreted and the results were analyzed separately. If first EEGs were excluded due to sedation, the first sedation-free EEG was considered to be the first ‘valid’ recording.

Statistical analysis was carried out where appropriate using SPSS software. Special focus was given to EEGs showing GPDs. The dependence of this pattern on clinical variables (e.g. length of hypoxia, cause of cardiac arrest) was calculated separately (multiple univariate analysis using Fisher’s Exact test- and Mann-Whitney U tests). Also the dependence of the dichotomized outcome (death /survival) on various clinical/EEG-Parameters was calculated using the X^2 -tests. Additionally the Odds ratio (OR) was calculated including Confidence interval (CI), where appropriate.

The Significance level was initially set at p=0.05. Because of multiple univariate testing, we divided the significance level through the number of tests (the dependence of GPDs on 13 parameters and the dependence of the dichotomized outcome on 12 parameters) to correct for multiple comparisons (Bonferroni correction). Sensitivity and specificity of each of the above named EEG patterns in predicting the outcome was calculated separately.
We also performed binary logistic regression with 1) the presence of GPDs (yes/no) as a dependent variable and 2) with outcome (dead/survived) as dependent variable. In each case we included the variables which proved to be significant in our previous analysis (after Bonferroni correction) as covariables.

This study was approved by the ethical committee of the Canton of Zurich. It complies with the Declaration of Helsinki.

Results:

1. Demographic and clinical characteristics of the study population

We identified 131 patients in our database of ICU EEGs, who obtained a standard EEG within the first two weeks after a CPR. Twelve patients had to be excluded, because no sufficient documentation of circulatory and/or respiratory arrest (no initial monitoring data) was available. The final sample size was 119 Patients (36 f / 83 m) with an average age of 60.4±15.5 years (Table 1). Forty-five (37.5%) patients suffered cardiac arrest due to myocardial infarction, while 20 (16.8%) suffered from non-ischemic heart disease. Other frequent reasons leading to secondary cardiac arrest were asphyxia (10.1%, n=12), traumatic injury (5.0%, n=6), hypovolemic shock (5.0%, n=6).

4.2% of the patients experienced cardiac arrests lasting between 3 and 5 minutes, 32.8% between 5 and 20 minutes and 42.0% longer than 20 minutes.

Fifty-five (46.2%) patients were treated with mild hypothermia for at least 24 hours immediately after the event.

Only three patients were treated with primary antiepileptic drugs at the time of the recordings: Valproic acid, topiramate and phenytoin respectively were used, where status epilepticus was considered as a differential diagnosis. Twenty patients were sedated with propofol and/or midazolame at the time of the EEG recording.

Ninety-two (77.3%) patients died within the first month. Out of 27 (22.7%) surviving patients, 10 (8.4%) patients were severely impaired, while 17 (14.3%) patients were comparatively slightly or moderately affected.

The first EEG was performed on average 3.8±3.0 days (range: 0 - 14 days) after CPR, with four (3.4%) recordings within 24h, 48 (40.3%) recordings in between 24 and 72 h and 67(56.3%) of the recordings >72 h after CPR. The majority of the patients (64.7%, n=77) were in a deep comatose state (GCS=3) during these recordings. Twenty-seven patients (22.7%) had repeated EEGs during their hospital stay (1 to 4 follow-ups). The second EEG was performed on average 7.5±4.9 days (range: 2 - 25 days) after CPR

Hundred (84.0%) patients also underwent cerebral imaging (either CT or MRI) with 45 (45%) of them showing signs of cerebral (cytotoxic) edema.

2. Main EEG findings in patients after CPR

The most frequent pathologic change in EEG was diffuse slowing (73.9%, with 24.4% in the theta-dominant and 49.6% in the delta-dominant range) (Table 1; all EEG Terminology used

according to ACNS (Hirsch LJ et al, 2013), see Material and methods). Thirty-five (29.4%) patients showed background suppression and 94 (79.0%) showed no reaction to external stimuli while 68 (57.1%) showed no variability of the background activity. Thirty-two (26.9%) of the patients had GPDs in the first EEG (Table 1). The frequency of discharges was between 0.5 and 2.5 Hz in most cases (87.5%; n=28) and no spatial or morphologic evolution of the periodic patterns was seen. Twenty-two of the patients who exhibited GPDs were given an i.v. bolus of midazolame during the EEG recordings, but only eleven of them showed a temporary suppression of GPDs.

Lateralized periodic discharges (LPDs) were seen in two patients (2%), and rhythmic delta activity (RDA) in thirteen (10.9%) (Table 1). Taken together, periodic discharges (GPD and lateralized periodic discharges) were seen in 28.6% of the EEGs.

Burst suppression patterns on the other hand were seen in 5 (4.2%) patients. We observed interictal epileptiform activity in 3 (2.5%) patients, and non-periodic generalized discharges with blunt triphasic morphology in 5 (4.2%) patients.

Half of the EEGs showing GPDs had a suppressed background (50%, n=16). Furthermore, most of the EEGs containing GPDs showed no background variability (78.1%, n=25) and virtually none showed reactivity to external stimuli.

In the group of patients with follow-up EEGs (n=27), 11 (40.7%) of the patients had GPDs (7 had GPDS in both recordings, while 2 had GPDs only in the first and another 2 patients only in the second recordings). This resulted in thirty-four patients, who had GPDs in at least one EEG (either first or follow up). The majority (n=14, 51.9%) of this subgroup did not show any changes in the second EEG. Six patients presented some change in the background activity (5 faster, 1 slower in the second EEG). Two out of the 5 patients showing increase in background frequency survived with minor deficits. Changes in background variability and reactivity were only seen in six patients.

GPDs were not significantly associated with the time interval between CPR and the first EEG recording (mean interval in the GPD group 3.1±1.7 days vs 3.9±3.3 days in the Non-GPD-Group, Mann-Whitney U, $p<0.795$). However all recordings showing GPDs were performed at least 24 h after CPR.

None of the patients showing GPDs had antiepileptic drugs at the time of the recordings.

In the group of patients under continuous sedation, seven of twenty patients (35.0%) showed GPDs, which was not significantly different from the non-sedated patients. Therefore there was no significant association of sedation and the occurrence of GPDs (Fisher's exact test *(F),* $p<0.171$).

On the other hand in the group of patients, who had been treated with mild hypothermia, half of the patients (50.9%, n=28) showed GPDs in their first recordings in contrast to only 6.3% (n=4) in the non-hypothermia group showing a significant association (*F,* p<0.0001).

Of all markers associated with the occurrence of GPDs (s. table 1) only hypothermia proved to be statistically independent in binary logistic regression (P<0.0001).

3. Electroencephalographic and clinical predictors of the outcome

All 32 patients with persistent GPDs in their first EEG (on average 3.8±3.0 after cardiac arrest) died within the first month - as compared to 69% in the non-GPD group, making this pattern a highly specific predictor of fatal outcome (see Table 2). Out of the group of patients, who showed persistent GPDs only in their second EEGs (n=2, EEG performed 6 and 12 days after CPR), one patient survived - with severe clinical deficits.

Other EEG patterns associated with unfavorable outcome were: Suppressed background (fatality rate 100%, n=35, *F*, p<0.0001) as well disturbed background continuity (fatality rate 93.6%, n=47, *F* p<0.001), non-variable background activity (fatality rate 89.7%, n=68, *F*, p<0.0003) and non-reactive background (fatality rate: 85.1%, n=94, *F*, p<0.0003). Four out of five patients with burst suppression patterns died (statistical analysis not performed due to small sample size). Rhythmic delta activity on the other hand, though it was only found in a comparatively small subgroup (n=13), was associated with a more favorable outcome (fatality rate 38.5%, *F*, p<0.00016). Out of the patient subgroup showing non-periodic generalized discharges with blunt triphasic morphology (n = 5) three survived. None of the patients showing LPD (n = 3) or non-periodic epileptiform discharges (n = 4) survived.

Among clinical variables, a comatose state during the time of recording was the strongest predictor of unfavorable outcome (fatality rate: 87.7%, n=77, *F*, p<0.001). Though there were significant differences of fatality rates between patients in comatose state with GPDs (100%, n=28) and those without GPDs (79.6%; n=49, *F*, p<0.011). Age on the other hand was not significantly associated with fatal outcome (fatality rate: 84.2% vs. 74.1% in patients < 70 yrs., p<0.218). All three patients, who were treated with AED, died.

None of the abovementioned significant predictors of outcome proved to be statistically independent in binary logistic regression. This was mainly due to the strong covariability of pathologic changes in EEG.

Discussion

We retrospectively analyzed EEGs of patients in the immediate aftermath of an episode of severe cerebral hypoxia due to cardiac arrest. Special focus was given to GPDs, which are assumed to be predictors of an unfavorable outcome (e.g. review by Bauer et al., 2013). While periodic discharges in ICU EEGs have been subject to numerous studies, comparatively few have separately assessed the significance of GPDs in hypoxic encephalopathy.

We could provide evidence, that GPDs according to the criteria of the ACNS is a frequently found pattern in the first EEG after cardiac arrest (in 26.9% of all cases, n=119). This retrospective study clearly supports the assumption, that in this patient population persistent GPDs are a highly specific predictor of fatal outcome (in our study in all cases, n=32). The outcome proved to be worse than in patients with GPDs of all etiologies (Foreman et al., 2012). It was also worse than described in more recent studies with GPDs in post cardiac arrest syndrome (Ruijter et al., 2015, Ribeiro et al., 2015). These differences in specificity might be due to different patient selection (no clinically apparent status epilepticus included, only patients with definite cardiac arrest in our case). Additionally more than half of the EEGs were recorded at least 72 hours after CPR, so that the early dynamic phase of changes in postanoxic EEG (Ruijter et al., 2015; Hofmeijer and van Putten, 2016) was not reflected in these measurements. Furthermore as standard EEGs were used in our study, intermittent appearance of GPDs could have been missed – in contrast to continuous monitoring. Particularly early transient GPDs are not necessarily associated with fatal outcome in all patients (Ruijter et al., 2015). Also the use of primary AEDs (in our case only in 3 patients) could play a confounding role.

Last but not least differences in definition of GPDs have to be taken into account. Whether GPDs constitute a subtype of non-convulsive status epilepticus (NCSE) remains unclear. Trinka et al. (Trinka et al., 2015) named classical GPDs with a frequency between 1-2.5 Hz “borderland of NCSE” and defined a relative limit of 2.5 Hz between classical GPDs and NCSE. Also the terms "subtle status" or “status epilepticus terminans” had already been coined in order to differentiate from classic NCSE (e.g. Hirsch et al., 2011). In the case of our study the majority of GPDs (87.5%, n=28) fell into the category between 0.5 and 2.5 Hz

discharges. Other distinctive features are complete lack of evolution in spacial distribution or time and no response to any currently available treatments (Trinka et al., 2015). The frequent occurrence of GPDs after therapeutic hypothermia in our study could at least partly be based on patient selection itself (hypothermia was only used in patients, who had had cardiac arrest for at least 10 Minutes). GPDs (or “periodic complexes”) have been described during hypothermia (Stecker et al., 2001). Body temperature was not systematically documented at the time of the recordings, but EEGs were always performed after warming up.

Other predictors of bad outcome were suppressed background and unresponsiveness to external stimuli which is well in line with previous studies (Ribeiro et al., 2015, Howard et al., 2012). On the other hand, we saw burst-suppression patterns only in 5% of the patients. Therefore the specificity of this typical encephalopathic EEG pattern could not be assessed sufficiently in our study.

The neurophysiologic correlate of GPDs is still a subject of debate. They are known to be associated with structural cortical and subcortical damage (Gloor, 1968). Recent studies highlight the importance of synaptic failure in the generation of periodic epileptiform discharges (Tjepkema-Cloostermans et al., 2014). In their review, van Putten et al (van Putten et al, 2015) state that GPDs are probably a correlate of selective synaptic failure and referred to a computational model of that assumption by Tjepkema-Cloostermans et al (Tjepkema-Cloostermans et al 2014). They point out that inhibitory interneurons are especially vulnerable to hypoxic stress, which leads to failure of feedforward inhibition. Authors generally agree on the notion, that (persistent) GPDs - in contrast to classic NCSE - represent severe and irreversible structural damage (van Putten et al., 2015, Foreman et al., 2012). The remarkably bad outcome of patients with persistent GPDs in our study supports this assumption.

There are several limitations to this study. Firstly as it is a retrospective study, the information gained from the EEGs could have influenced clinical decisions. E.g. decisions as whether to carry on with life supporting measures were potentially (but by far not solely) influenced by these findings. Secondly not all patients admitted to the ICU with hypoxic encephalopathy had an EEG recorded and EEG recordings started at an average of 3.8 days after admission. As it is well-established that EEG patterns change significantly in the first few days, including appearance and disappearance of GPDs, the frequency of GPDs might have been even higher. Additionally EEG patterns are prone to different subjective interpretation by neurophysiologists, even if the same terminology is used. We tried to minimize this effect by using the very standardized protocol provided by the ACNS. As all pathologic changes in EEG tended to show strong covariability, binary regression analysis did not identify independent EEG-variables associated with fatal outcome. Nonetheless, if singled out, GPDs

and suppressed background showed the most significant results with regard to outcome prediction (table 2).

As Bauer et al (Bauer et al., 2013) pointed out, there is an evolution of encephalopathic changes in EEGs after a hypoxic event. Persistent GPDs presumably form a pre-terminal stage in this development. As there was no fixed time interval between hypoxia and EEG, early changes in EEG, as described by recent studies (Spalletti et al, 2016, Sivaraju et al 2015) would have been missed. On the other hand we did not find significant or consistent changes in the available follow-up EEGs in most cases (data not shown). Again, as the most dynamic EEG changes occur in the first 72 hours after cardiac arrest, and with the majority of recordings being performed later, this finding is not unusual.

However this does not alter the predictive value of EEG in hypoxic encephalopathy which was underlined in this study. It supports the assumption of persistent GPDs being an indicator of unfavorable outcome.

Conflict of interest statement: NONE

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Table 1: Characterization of the study cohort and main EEG findings

(*= Stat. significant after Bonferroni correction, significance level at 0.05/13=0.0036, AVG = Average, SD = standard deviation, *F* = Fisher's exact test, Stat = Statistical Method used, OR = Odds ratio, CI = Confidence interval based on X^2-distribution)

	GPDs	**No GPDs**	**Total number/AVG**	*P*<	Stat	OR (CI)
Total numbers: n (%)	32 (26.9)	87 (73.1)	119			
Age, mean ± SD	61.2±14.7	60.2±15.9	60.4±15.5	0.976	Mann-Whitney	N.A.
Female: n (%)	9 (28.1)	27 (31.0)	36 (27.7)	0.825	*F*	0.87 (0.36-2.13)
Death within 1 month: n (%)	32 (100)	60 (69.0)	92 (77.3)	**0.0001***	*F*	N.A.
Primary cardiac disease: n (%)	23 (71.9)	42 (48.3)	65 (54.6)	0.024	*F*	2.74 (1.14-6.59)
Length of cardiac arrest >20 min: n (%)	20 (62.5)	30 (34.5)	50 (42.0)	0.011	*F*	2.61 (1.12-6.11)
Interval between CPR and EEG (days), mean ± SD	3.1±1.8	3.9±3.3	3.7±3.0	0.795	Mann-Whitney	N.A.
Sedation: n (%)	7 (21.9)	13 (14.9)	20 (16.8)	0.171	*F*	1.59 (0.57-4.44)
Hypothermia: n (%)	28 (87.5)	27 (32.0)	55 (46.2)	**0.0001***	*F*	15.56 (4.97-48.73)
Main EEG findings						
General slowing	17 (53.1)	71 (81.6)	88 (73.9)	0.004	*F*	0.26 (0.11-0.62)
Theta-dominant	3 (9.4)	26 (29.9)	29 (24.4)			
Delta-dominant	14 (43.8)	45 (51.7)	59 (49.4)			
Background voltage < 10 uV	16 (50.0)	19 (21.8)	35 (29.4)	0.006	*F*	3.57 (1.52 - 8.46)
Background nonvariable *[2]	25 (78.1)	43 (49.4)	68 (57.1)	0.006	*F*	3.65 (1.43 - 9.33)
Background nonreactive to stimuli *[2]	32 (100)	62 (71.3)	94 (79.0)	**0.0002***	*F*	N.A.
Disturbed background continuity *[2]	21 (65.6)	26 (29.9)	47 (39.5)	**0.0006***	*F*	4.48 (1.89 - 10.60)

Table 2: Correlation of clinical parameters and EEG patterns with the outcome

(**= Stat. significant after Bonferroni correction, significance level at p=0.05/12=0.004;* S= *Sensitivity in %; percentages in column "died" correspond to specificity for fatal outcome, P= according to Pearson's X²-test,* Stat = Statistical Method used, OR =Odds ratio, *F* = Fisher's exact test, CI = Confidence interval based on X²-distribution)

	Survived	**Died**	**Total**	*P* (death/ survival)	**S**	**Stat**	**OR (CI)**
Total numbers: n (% of row sum)	27 (22.7)	92 (77.3)	119				
Demographic and Clinical Parameters:							
Female	11 (30.6)	25 (69.4)	36	0.233	27.1	*F*	0.54 (0.22 - 1.33)
Age >70	6 (15.8)	32 (84.2)	38	0.250	34.8	*F*	1.87 (0.68 – 5.09)
Cardiac arrest >20 min	5 (10.0)	45 (90.0)	50	0.007	48.9	*F*	4.21 (1.47 - 12.08)
Comatose	10 (14.1)	67 (85.9)	77	**0.001***	72.8	*F*	4.56 (1.84-11.28)
Hypothermia performed	11 (20.0)	44 (80.0)	55	0.661	47.8	*F*	1.33 (0.56 – 3.18)
Sedation	3 (15.0)	17 (85.0)	20	0.559	16.8	*F*	1.81 (0.49 – 6.72)
Signs of cerebral oedema in CT/MRI	4 (8.9)	41 (91.1)	45	0.023	50.6	*F*	4.62 (1.48 – 14.43)
EEG Parameters:							
GPDs	0 (0)	32 (100)	32	**0.0001***	34.8	*F*	N.A.
Background voltage < 10 uV	0 (0)	35 (100)	35	**0.0001***	38.0	*F*	N.A.
Background nonvariable	7 (10.3)	61 (89.7)	68	**0.0003***	66.3	*F*	5.45 (2.08 – 14.24)
Background nonreactive to stimuli	14 (14.9)	80 (85.1)	94	**0.0003***	87.0	*F*	6.19 (2.35 – 16.30)
Disturbed background continuity	3 (6.4)	44 (93.6)	47	**0.001***	47.8	*F*	7.33 (2.06 - 26.06)